Jörg Gölz

Understanding and living with HIV

HIV is a virus that reproduces within the human immune system.

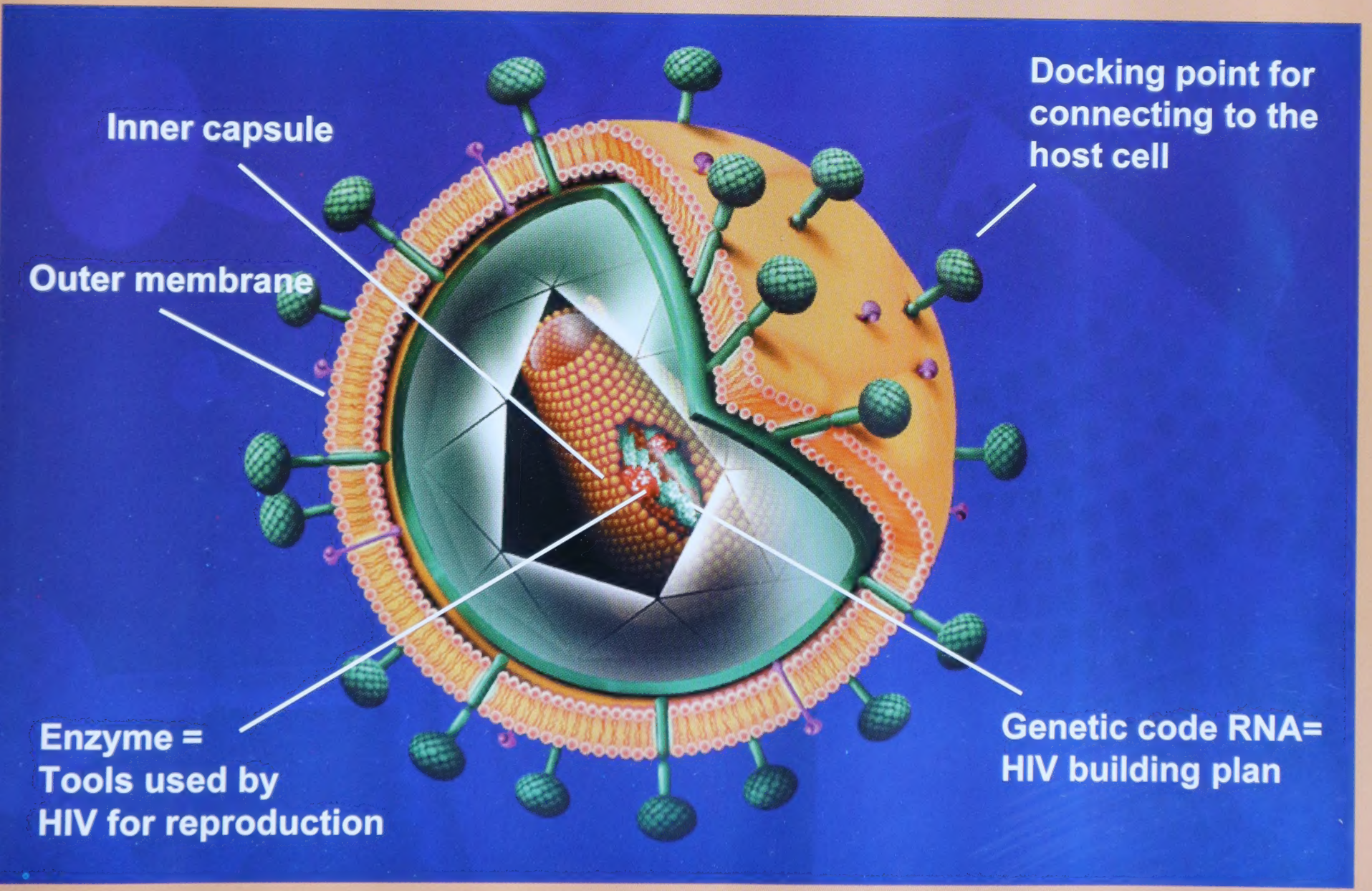
HIV(Human Immune Deficiency Virus) is a virus. As with all viruses HIV cannot exist independently. It needs a human host cell in order to reproduce. Similar to a parasite HIV misuses the metabolism of the infected host cell in order to survive within the human body.

Humans can only be infected by HIV through certain contact with bodily fluids that contain high levels of the virus (blood, semen, vaginal secretions and breast milk). The risk of becoming infected is highest through unprotected sex or in the case of drug users through sharing contaminated needles.

The structure of the virus is relatively sim

- an **outer membrane with docking nc**
- an **inner capsule** that contains the bu so known as the **genetic code** or viral RNA.
- certain tools, **enzymes** which organise

The human cells used by HIV as host ce are an essential part of the immune system.


Inner capsule
Outer membrane
Docking point for connecting to the host cell
Enzyme = Tools used by HIV for reproduction
Genetic code RNA= HIV building plan

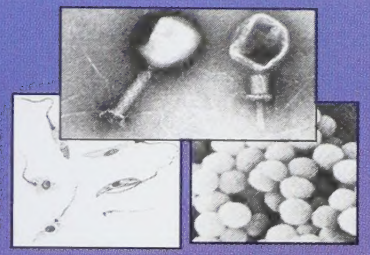
The immune system protects against infection

The immune system is a complicated mechanism within the human body that protects against infection. It is made up of different groups of cells that are comparable to an army's defence troops. Through complex interactions they control the body's defence against enemy invaders (bacteria, parasites, viruses) that the outside world confronts us with 24 hours a day.

One line of defence are the killer cells. They directly attack and destroy invaders. A further special unit is made up of B-cells that are a sort of health police within the body. The B-cells mark and paralyse invaders using antibodies, thus making the invaders easy prey.

The CD4 helper cells are the headquarters of the immune system. They give out the orders to the other defenders and direct them into action. This makes the CD4 helper cells an irreplaceable part of the immune system.

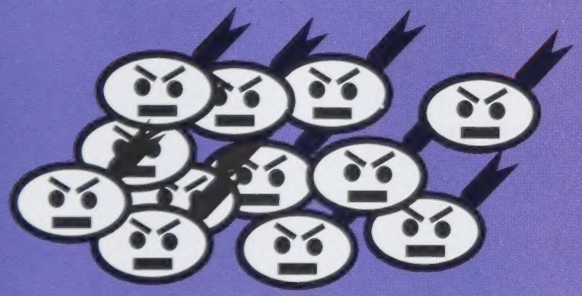
An optimally functioning immune system with well prepared defenders is thus in a position to fight disease-causing agents quickly and effectively.



Bacteria, Viruses,
Parasites
"Terrorists"

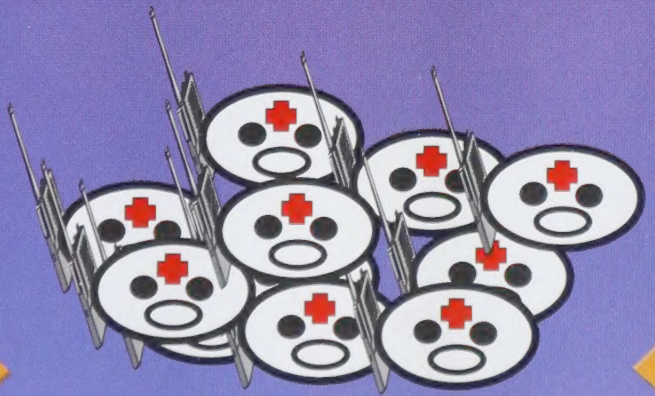
Attack

Attack



Killer cells
"Special units"

B-Cells with antibodies
"Health police"



CD4 helper cells
"Headquarters"

Marching orders

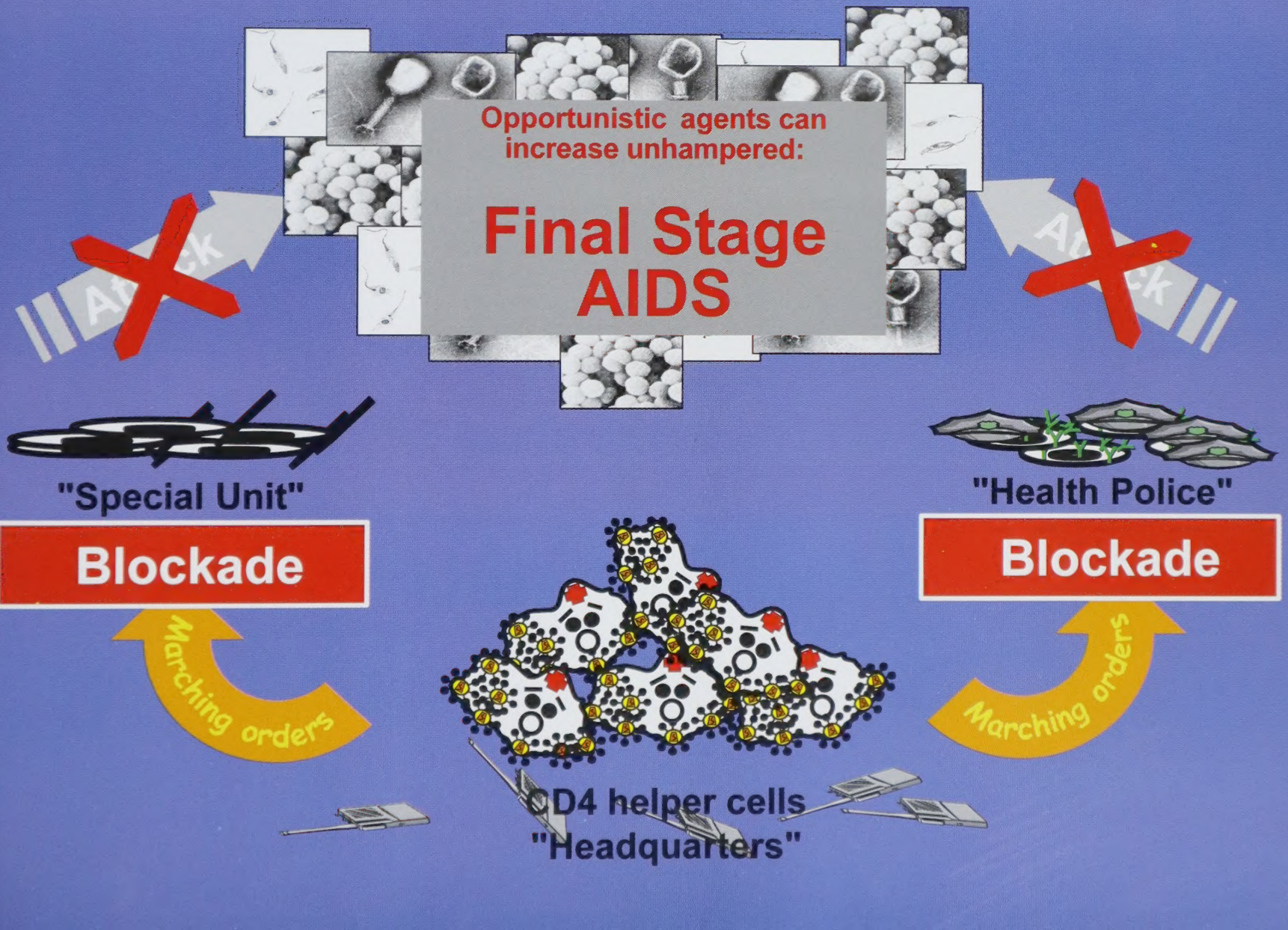
Marching orders

HIV damages the immune system and destroys the body's protection against opportunistic infections

Unfortunately HIV operates by taking over and destroying the immune system's headquarters. It reproduces within and thereby destroys the CD4 cells whose task is to control the defenders.

Once the immune system is compromised by the loss of CD4 cells the body is in grave danger. Invaders which the body normally keeps in check without us noticing can become life threatening.

These life threatening invaders can go on to become illnesses (e.g. certain types of lung infection = PCP, toxoplasmosis, tuberculosis etc.). These illnesses, also known as opportunistic infections, are grouped under the term AIDS.


Opportunistic agents can increase unhampered:
Final Stage AIDS
"Special Unit"
Blockade
Marching orders
"Health Police"
Blockade
Marching orders
CD4 helper cells
"Headquarters"

HIV reproduces within the CD4 helper cells in the immune system

❶ HIV recognises its host cells, the CD4 helper cells, and **docks onto them**

❷ HIV penetrates the human immune cell (**fusion**). Once there it releases its genetic code (RNA) and its own enzymes

❸ Using one of its enzymes, the **reverse transcriptase**, HIV adapts its genetic code to that of the human cell

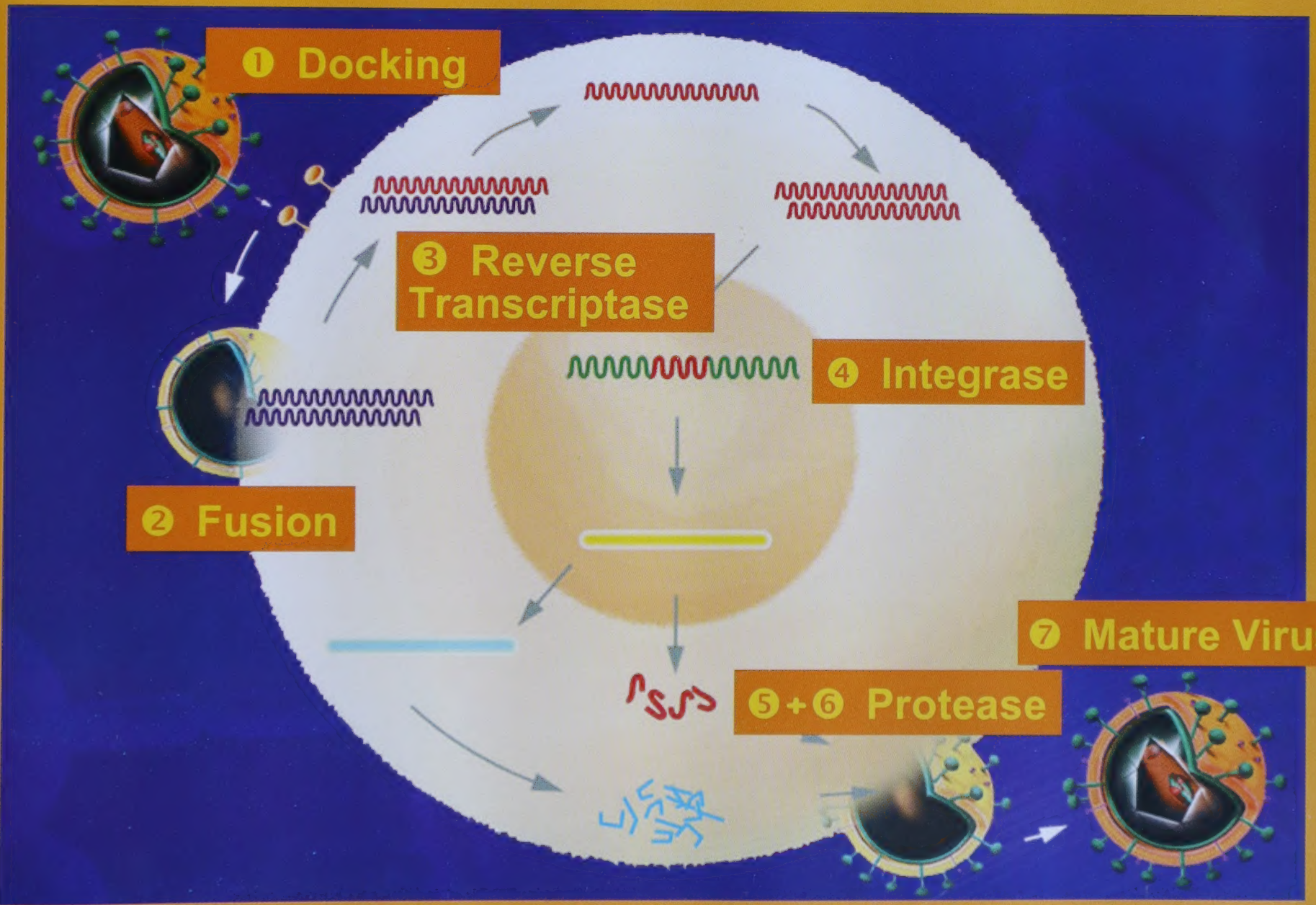
❹ A second enzyme, the **integrase**, inserts the viral genetic code into the human genetic code. This causes the CD4 helper cell to become infected and is from then on used by the virus as a base for its own reproduction.

❺ The individual components of the virus are altered by the **protease** and the virus is formed.

❻ The virus is ejected out of the CD4 helper cell. During this process some of its components are completed. This step of the process for which the **protease** is needed is also called the the viral maturation stage.

❼ The completed **"mature virus"** is now ready to infect other CD4 helper cells.

During HIV's reproduction process the CD4 helper cell is damaged so much that it dies.


1 Docking
2 Fusion
3 Reverse Transcriptase
4 Integrase
5+6 Protease
7 Mature Virus

HIV reproduces millions of times a day if no medication is taken

Every day millions of new viruses are produced. The amount of HIV contained in the blood can be measured and is called the viral load. A high viral load means that a lot of the virus is in the blood and that HIV is active and reproducing rapidly.
The following diagram shows the development of the viral load during the course of infection in an untreated HIV patient:

❶ Immediately following an infection with HIV the viral load is high. The immune system is still fully engaged and fights the virus reducing the viral load.

❷ For a long period of time the viral count in the blood remains constant as a balance is reached between the viral production and the immune systemís defence.

❸ During the latter course of the infection the immune system weakens further as HIV reproduces uninterrupted and the viral load increases.

The immune system can no longer fight HIV on its own, it needs reinforcement through medication.


Viral load
1
2
3
Time

The development of the CD4 cell count in untreated patients

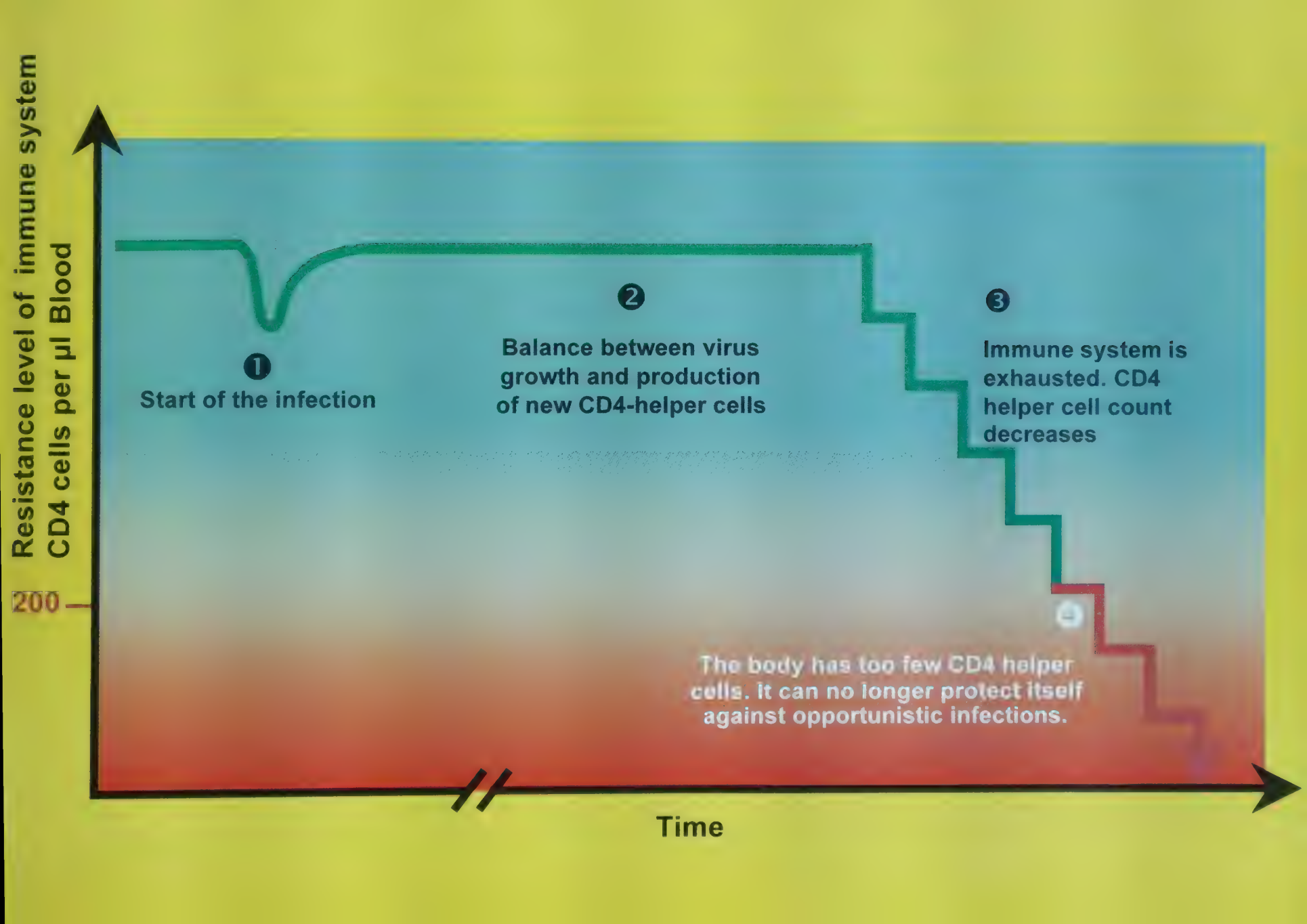
The number of CD4 helper cells is a measurement of the strength of the body against disease-causing agents. The following diagram shows the development of the CD4 helper cell count in an *untreated* patient during the course infection by HIV:

❶ HIV penetrates the CD4 cells and and in the course of reproduction destroys them. This leads to a decrease in the CD4 cell count during the initial stage of infection.

❷ The immune system remains functional and can defend itself against HIV. The virus continues to reproduce within the CD4 cells reducing them. Despite this the immune system can still supply reinforcements by producing new CD4 helper cells. This is why the CD4 helper cell count remains constant for a relatively long time.

❸ However this heightened production of new CD4 cells eventually depletes the immune systemís reserves - it can no longer keep up the production - resulting in a decreased CD4 cell count.

❹ The weakened immune system with fewer CD4 cells can no longer defend the body against opportunistic diseases. PCP lung inflammation, tuberculosis, toxoplasmosis, herpes viruses and other life threatening illnesses can develop. Doctors call this final stage AIDS.


Resistance level of immune system
CD4 cells per µl Blood
200
1
Start of the infection
2
Balance between virus growth and production of new CD4-helper cells
3
Immune system is exhausted. CD4 helper cell count decreases
4
The body has too few CD4 helper cells. It can no longer protect itself against opportunistic infections.
Time

The aims of antiretroviral therapy

The most important aim of the therapy is to increase the CD4 cell count in the blood and thus the **recovery of the immune system**.

To do this the **virus reproduction must be inhibited**.

Two measurements are important in telling whether or not the therapy is working:

- The viral load, i.e. the amount of virus in the blood: this shows whether or not the virus is being successfully fought. The viral load is always measured as the number of virus per millilitre of blood. In general your doctor will measure the viral load every 2 to 3 months. Sometimes it is necessary to do this more frequently, for example when switching to other medication.
- The number of CD4 helper cells in the blood shows whether or not the immune system is recovering. The CD4 helper cell count is also generally measured every 2 to 3 months. It is measured as the number of CD4 helper cells per millilitre (=1/1000 ml) of blood.

Inhibiting the virus increase:

Reduction of the viral load

Antiretroviral therapy

Recovery of the immune system:

Increase of the CD4 helper cell count

Antiretroviral therapy

Antiretroviral medicines paralyse HIV's tools

Antiretroviral medicines attack the tools that HIV needs for its reproduction. These tools are also known as enzymes.

In current therapies both the **REVERSE TRANSCRIPTASE** and the **PROTEASE** HIV enzymes are inhibited.

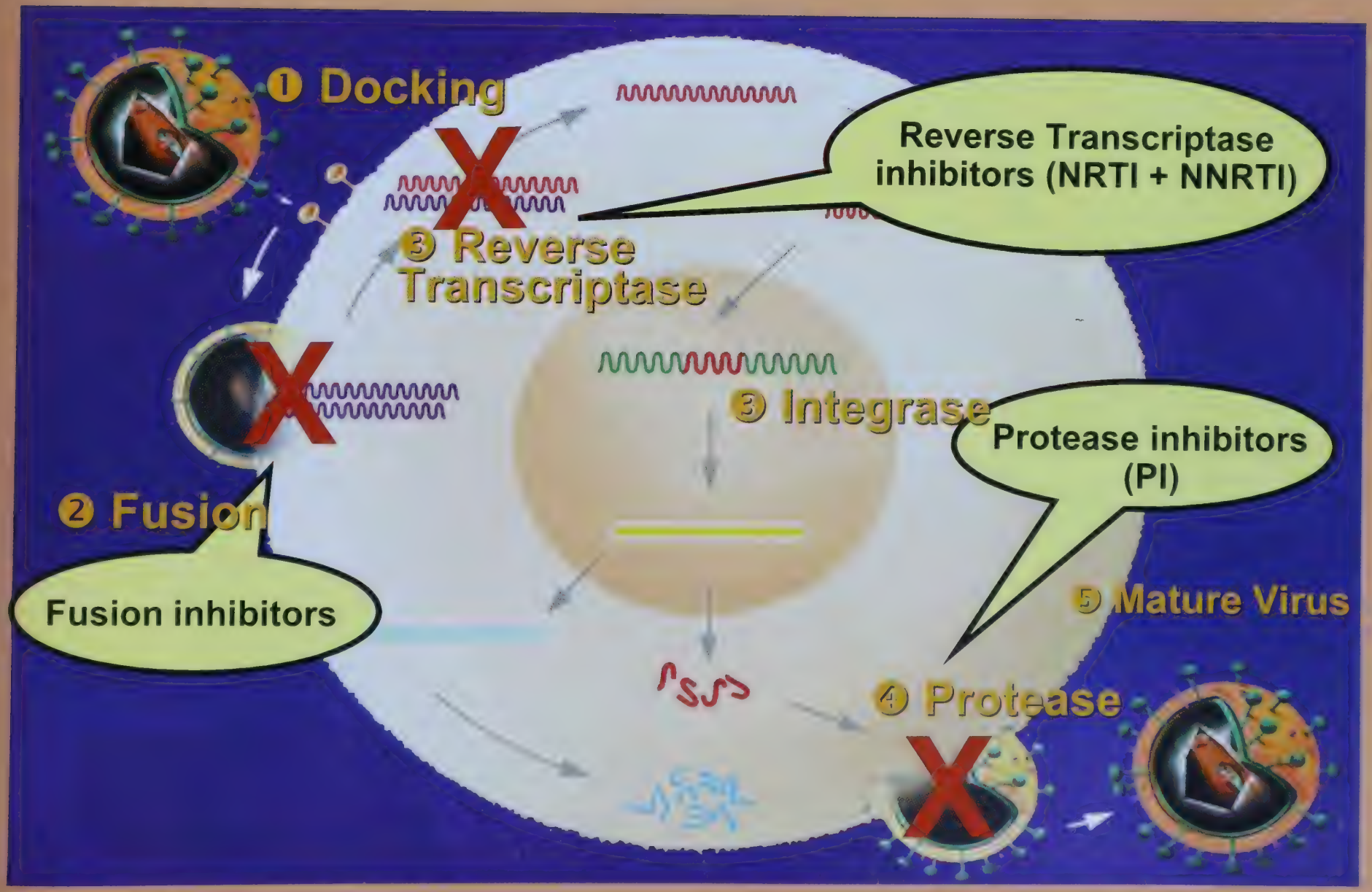
This is why we differentiate the antiretroviral group of medicines into:

- **REVERSE TRANSCRIPTASE INHIBITORS**, which in turn are divided into Nucleoside Analogue (NRTI) and Non-Nucleoside Analogue (NNRTI).
- **PROTEASE INHIBITORS** also known as PI.

The medicines stop the activity of the corresponding enzymes. Without active enzymes HIV cannot reproduce.

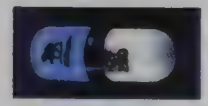
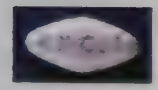
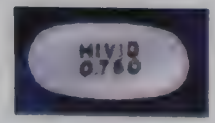
New treatment approaches will also be offered by **FUSION INHIBITORS.** They stop the HIV from penetrating the cells.

The more medicines that attack the virus the more difficult it is for HIV to get the upper hand. This is why combinations of multiple HIV medicines are currently used.

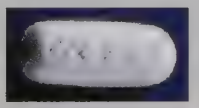
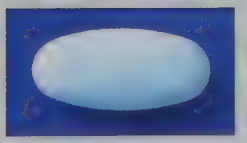

1 Docking
Reverse Transcriptase inhibitors (NRTI + NNRTI)
3 Reverse Transcriptase
3 Integrase
Protease inhibitors (PI)
2 Fusion
Fusion inhibitors
5 Mature Virus
4 Protease

Which medicines are available?

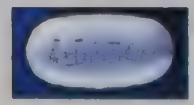
Nucleoside Analogue Reverse Transcriptase Inhibitors (NRTI)

Product Name	Active Ingredient	Abbrev.	Picture	Standard Dose	Prescribed Dose
Retrovir®	Azidothymidin	AZT		2x1 (à 250 mg) Capsule	
Epivir®	Lamivudin	3TC		2x1 Tablet	
Videx®	Didanosin	ddI		1x1 (à 400 mg) Capsule	
Hivid®	Zalcitabin	ddC		3x1 Tablet	
Zerit®	Stavudin	d4T		2x1 Capsule	
Ziagen®	Abacavir	ABC		2x1 Tablet	

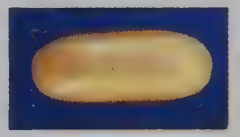
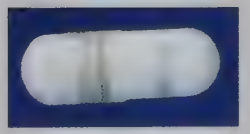
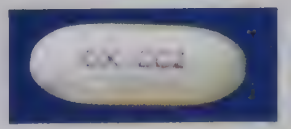
Nukleoside Analogue Reverse Transcriptase Inhibitors (NRTI)

Product Name	Active Ingredient	Abbrev.	Picture	Standard Dose	Prescribed Dose
Combivir®	Azidothymidin Lamivudin	CBV		2x1 Tablet	
Trizivir®	Azidothymidin Lamivudin Abacavir	TZV		2x1 Tablet	

Non-Nucleoside Analogue Reverse Transcriptase Inhibitors (NNRTI)

Product Name	Active	Abbrev.	Picture	Standard Dose	Prescribed Dose
Viramune®	Nevirapin	NVP		2x1 Tablet	
Rescriptor®	Delavirdin	DLV		3x4 Tablets	
Sustiva®	Efavirenz	EFV		1x3 Capsules	

Protease Inhibitors (PI)

Product Name	Active Ingredient	Abbrev.	Picture	Standard Dose	Prescribed Dose
Fortovase®	Saquinavir	SQV		3x6 Capsules	
Crixivan®	Indinavir	IDV		3x2 Capsules	
Viracept®	Nelfinavir	NFV		2x5 Tablets	
Agenerase®	Amprenavir	APV		2x8 Capsules	
Norvir®	Ritonavir	RTV		2x6 Capsules	
Kaletra®	Lopinavir + Ritonavir	LPV + RTV		2x3 Capsules	

Antiretroviral therapy is a combination therapy

The antiretroviral medication available today is combined to form an effective therapy. In general three active ingredients are currently prescribed together to combat HIV. The number of active ingredients are not always the same as the number of medicines that you may be prescribed. Sometimes a medicine is already made up of more than one active ingredient.

With some medicines you have to follow certain nutritional rules. Some medicines are not absorbed by the body well enough if taken along with foods that contain too much or too little fat. Some medicines must be taken with a lot of liquids.

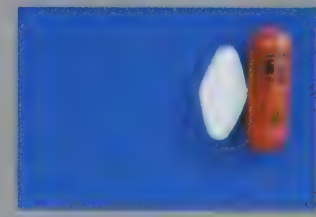
All medicines that are currently available have certain advantages and disadvantages. Some may have side-effects that you cannot tolerate. Some may interact with other medication you may be taking.

Your doctor will discuss with you the combination best suited to you. You should try together with your doctor to find a therapy that best fits in with your daily routine. This helps guarantee your ability to take the medication regularly.

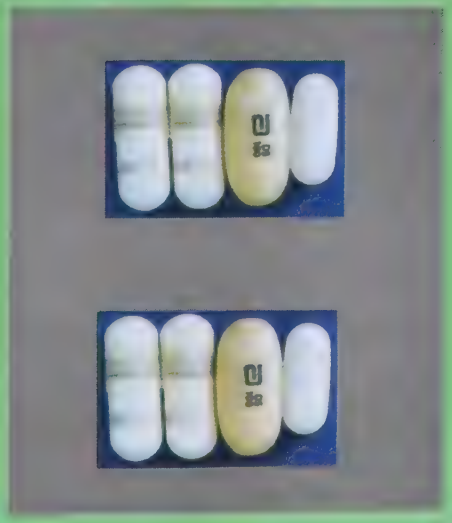
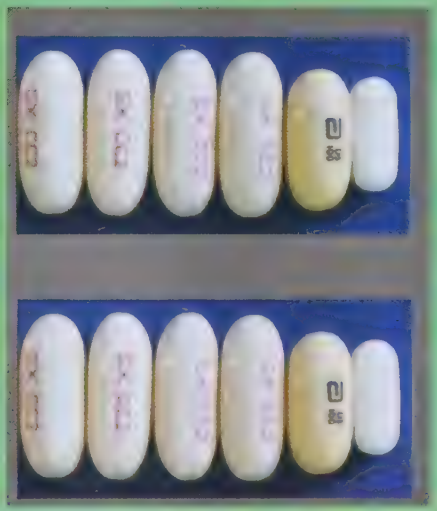
Examples of triple NRTI combination therapies

	Example 1	Example 2	Example 3
	Trizivir®	Ziagen® + Epivir® + Zerit®	Ziagen® + Videx® + Zerit®
Mornings			
Evenings			

Examples of combination therapies with 2 NRTI and 1 NNRTI

	Example 1 Combivir® + Viramune®	**Example 2** Videx® + Zerit® + Sustiva®	**Example 3** Epivir® + Zerit® + Sustiva®
Mornings			
Evenings			

Examples of combination therapies with NRTIs and PIs

	Example 1 Combivir® + Crixivan® + Norvir®	Example 2 Videx® + Zerit® + Viracept®	Example 3 Combivir® + Norvir® + Agenerase®
Mornings			
Evenings			

HIV can only be inhibited if the medication concentration is high enough

The success of an antiretroviral therapy is highly dependent on the medication being taken regularly.

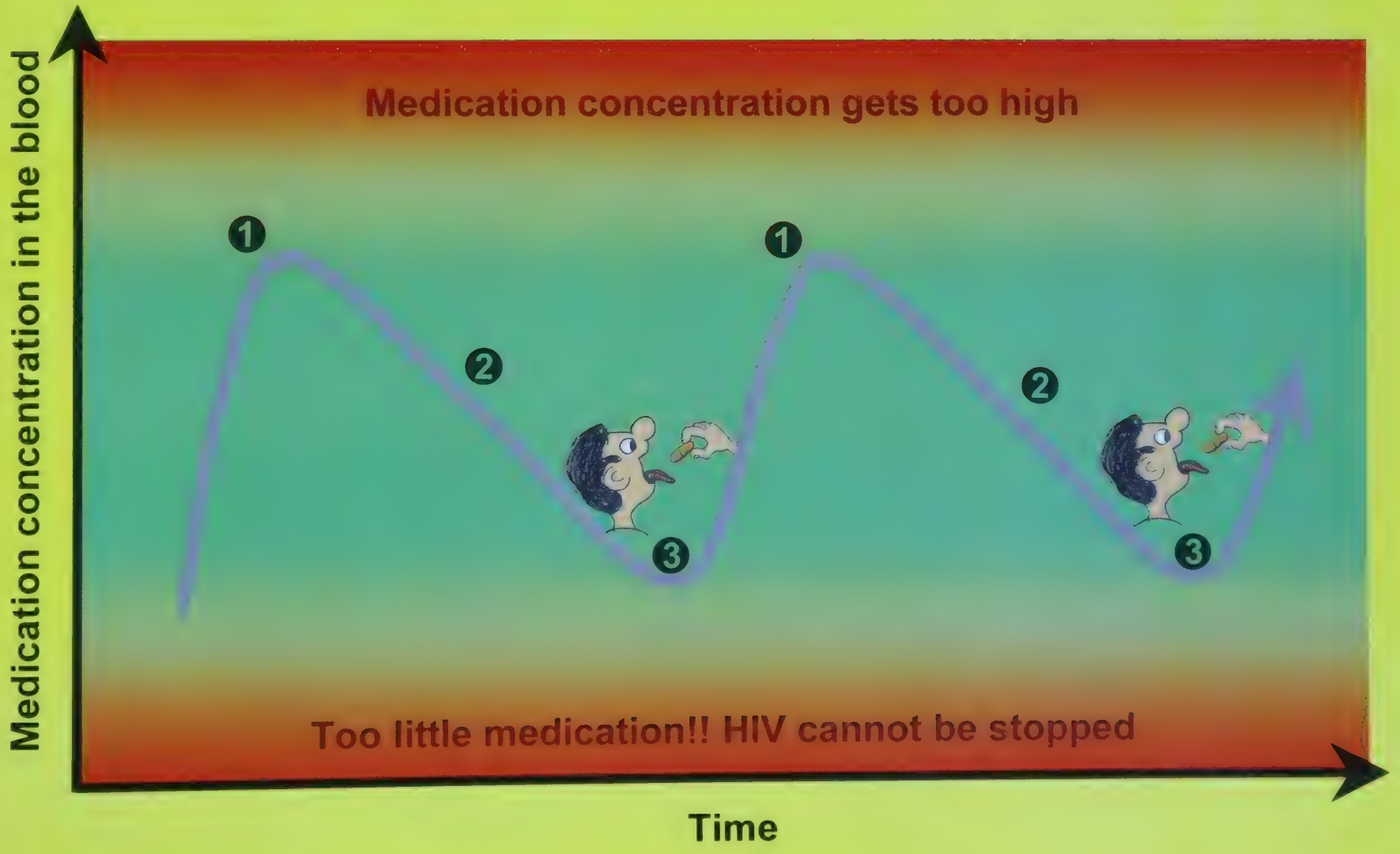
❶ Shortly after taking the medication the concentration is at its maximum.

❷ The medication is broken down in the body and the concentration decreases.

❸ Time for the next dose so that the level of medication in the blood does not sink too low. HIV cannot be slowed if the level of medication in the blood is too low!

The frequency with which medication needs to be taken depends on its composition. Medication that is only broken down slowly by the body need only be taken twice or sometimes even only once a day.

Should you forget to take a dose you should not take a double amount to make up for the missed one the next time around. If you take a dose higher than that prescribed by your doctor the medication may reach intolerable levels within your blood.


Medication concentration in the blood
Medication concentration gets too high
1
2
3
1
2
3
Too little medication!! HIV cannot be stopped
Time

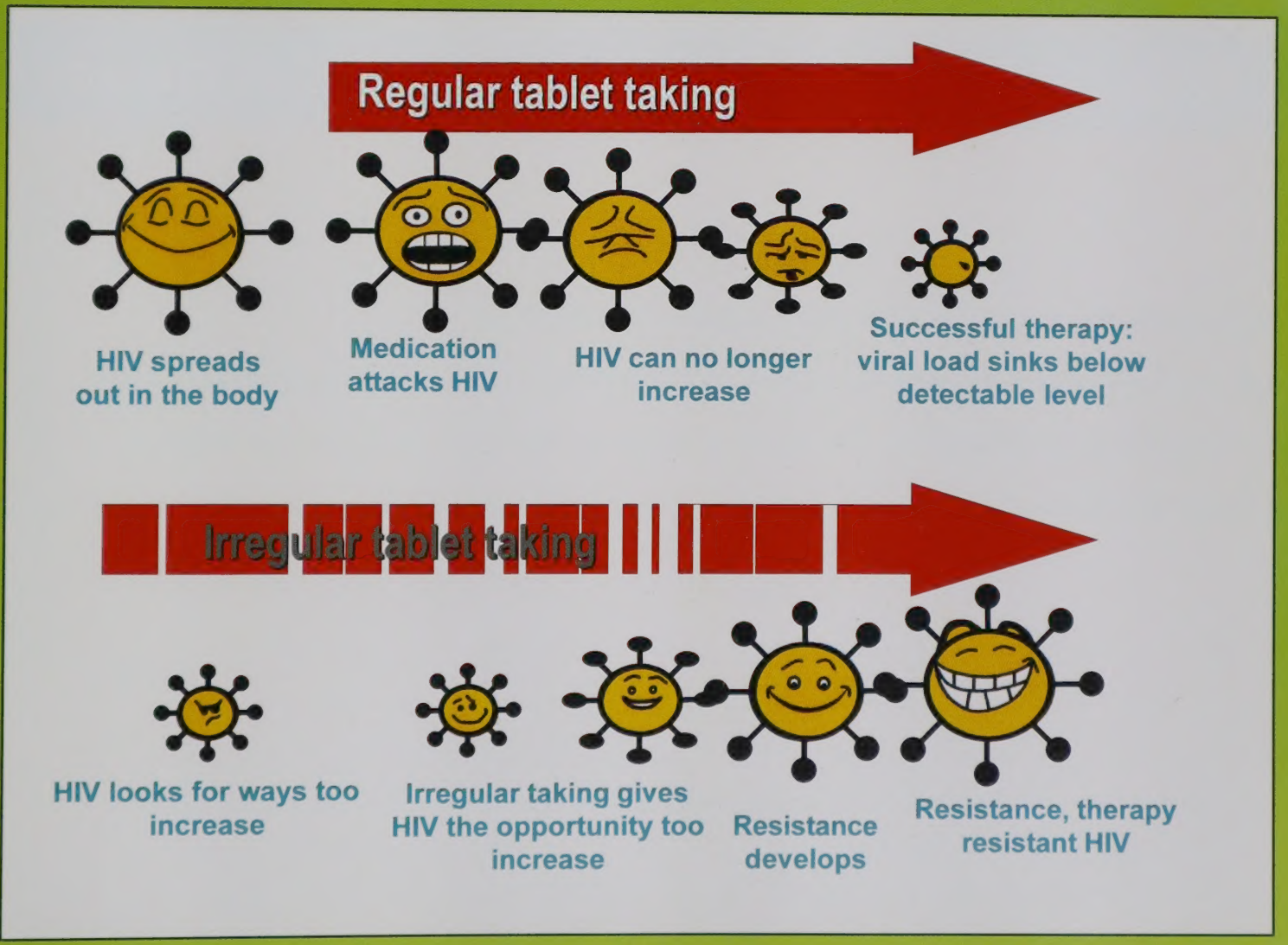
HIV resistance can be avoided if there is always enough medication in the blood

HIV can adapt to antiretroviral medication. This is known as RESISTENCE.

The virus can multiply and become resistant when the concentration of medication in the blood is too low.

Critical factors that can lead to a low blood concentration of the medication:

- Disruption of the take up of the medication by the body (e.g. diarrhoea, vomiting etc.)
- Irregular taking
- Not taking medication as instructed (e.g. taking together with too much, too little or with the wrong foods).



Change in accordance with Erickson et al., Aids Supl. 1999: Protease inhibitors: resistance, cross-resistance, fitness and the choice of initial and salvage therapies

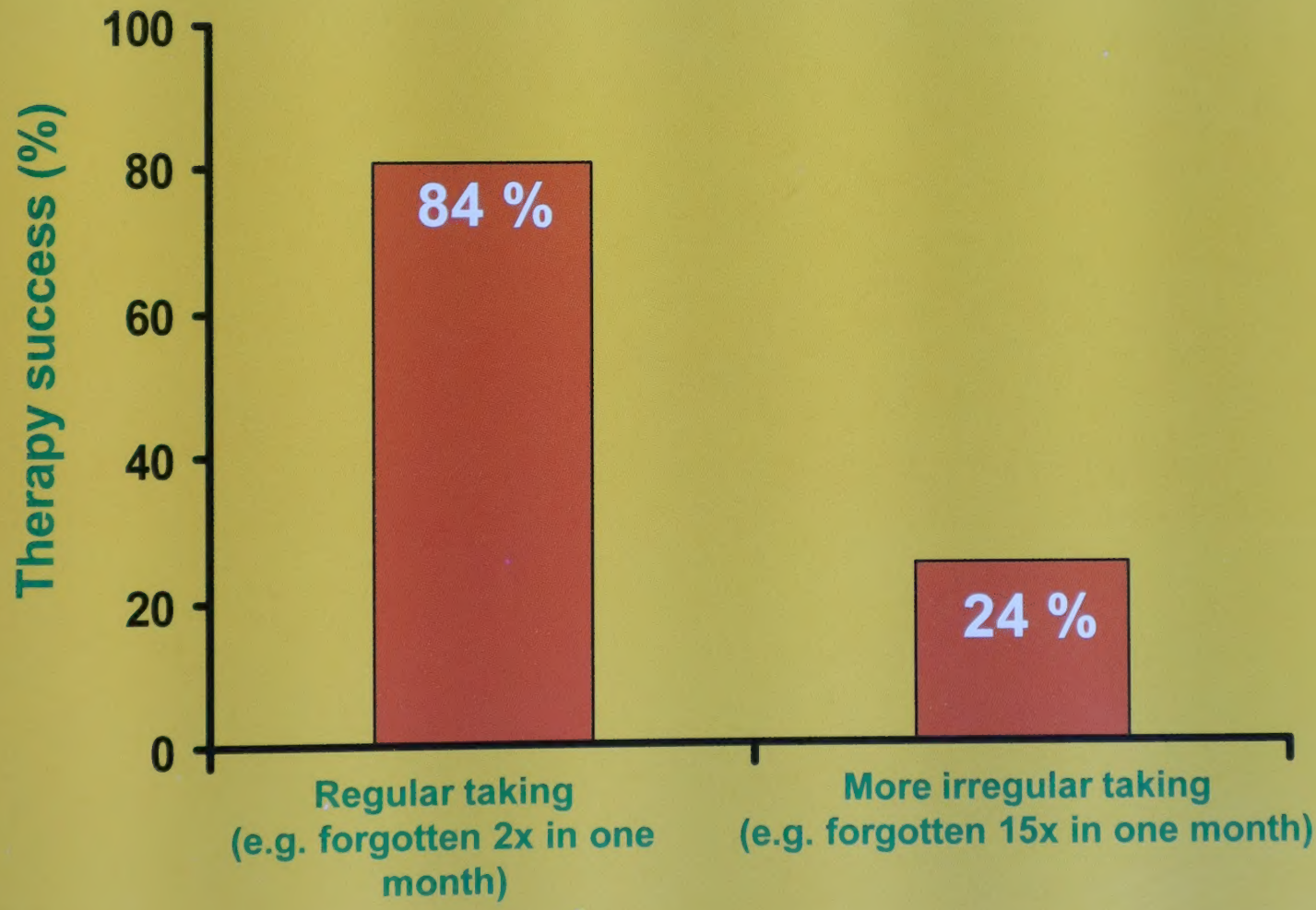
Regular tablet taking leads to successful therapy

Taking medication regularly protects against resistance.

A high enough concentration of active ingredients in your body suppresses HIV.

This makes it very difficult for the virus to build up resistance to the medication.

The virus remains responsive to therapy. The medication continues being effective against HIV.



Changed in accordance with Paterson et al.: 6th CROI, Chicago, February 1999. Abstract 092

Interested in more information?

gsk GlaxoSmithKline

Idea and concept: Martina Heinze, Christina Schröder, Klaus Heintz

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